REMARKS

Claims 1-36 are pending in the application and stand rejected. Claims 1, 2, 5, 8, 9, 13-15, 17, 23, 26, 29, 30, 33, and 34 have been amended. Claims 37-43 have been added. Claims 35, 36, and the second occurrence of Claim 34 have been canceled. Reconsideration and allowance of Claims 1-34 and 37-43 in view of the above amendments and following remarks is respectfully requested.

The Rejection of Claims 1-36 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-36 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Withdrawal of the rejection is requested for the following reasons.

The Examiner states that the recitation of "ester or prodrug thereof" in Claim 1 renders Claim 1 and its dependent claims indefinite. Although applicants respectfully disagree with this rejection, in order to expedite examination, Claim 1 has been amended by deleting the phrase "ester or prodrug." In view of the amendment to Claim 1, withdrawal of the rejection is respectfully requested.

Claim 34 is recited twice in the claims. The second occurrence of Claim 34 has been deleted.

Claims 35 and 36 relate to uses of compounds of formula I. Claims 35 and 36 have been canceled.

The Rejection of Claims 1-36 Under 35 U.S.C. § 112, First Paragraph

Claims 1-36 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for salts of the claimed compounds, does not reasonably provide enablement for prodrug or esters of the claimed compounds. Although applicants respectfully disagree with this rejection, in order to expedite examination, Claim 1 has been amended by

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deleting the recitation "prodrug or ester." In view of the amendment, withdrawal of the rejection is respectfully requested.

The Rejection of Claims 26-36 Under 35 U.S.C. § 112, First Paragraph

Claims 26-36 stand rejected under 35 U.S.C. § 112, first paragraph. Specifically, it is asserted on pages 6-7 of the Office Action, *inter alia*, that Claims 23-34 (Claims 35-36 have been canceled) fail to meet the enablement and written description requirements because they are purportedly "drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions for which they lack written description and enabling disclosure." Applicants respectfully traverse this rejection for the following reasons.

The Office Action acknowledges that the compounds of the present invention are mechanistic inhibitors of PI3-kinase and are enabled for the treatment of breast cancer, but allegedly not for "any or all cancer or any or all proliferative capillar[y] diseases due to phosphotidylinositol (PI)-3-kinase inhibition including those yet to be discovered." To support the rejection the Office Action describes a number of different types of cancers, tumors, and proliferative diseases and surmises, "no compound has ever been found to treat proliferative diseases of all types generally." Although applicants agree with the Examiner that no single drug has been approved fur use against any and all forms of cancer, that is not dispositive or even relevant in determining compliance with the enablement or written description requirements under 35 U.S.C. § 112. "The Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States." MPEP § 2107.01. Applicants have shown significant PI3-kinase inhibitory activity of the presen6tly claimed compounds and that PI3-K expression is implicated in a number of different cancers, tumors, and proliferative

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diseases. That there conceivably exist cancers from which Pi3-K is not implicated does not render the claims non-enabled or without written description.

"The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. Modern science has previously identified numerous successful chemotherapeutic agents." In re Brana, 51 F.3d 1560. Applicants have described a biochemical assay for screening compounds of Formula (1) and described results showing their activity therein. Additionally, applicants have provided description of PI3-K in processes associated with cancer and other disorders including mitogenesis, oncogenesis, histamine secretion, neutrophil activation, platelet activation, cell migration, glucose transport, antilipolysis, and vesicle sorting (Pages 2-3 of the present application. References such as Cantley et al., *Cell 64*:281-302, 1991 and Escobedo et al., *Nature 225*:85-87, 1998, were also cited in the present application, which describe PI3-K and its association with SRC-like or receptor tyrosine kinases, implicated in oncogenic or mitogenic responses. Finally, applicants provided numerous methods for administration of the compounds of Formula (1) to a subject for which PI3-K inhibition is sought (see pages 47-54 of the specification).

"Any party making the assertion that a U.S. patent specification or claims fails, for one reason or another, to comply with 35 U.S.C. § 112 bears the burden of persuasion in showing said lack of compliance." *Fiers v. Revel*, 984 F2d 1164. the current rejection provides no specific evidence or basis for showing lack of enablement or written description for the claimed uses of compounds of Formula (1). Should the Examiner maintain that the present claims lack written description and enablement, it is respectfully requested that specific supporting evidence be made of record. Applicants respectfully submit that the instantly claimed invention fully complies with the written description and enablement requirements of the first paragraph of

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35 U.S.C. § 112. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of Claims 23-34 on these grounds.

Furthermore, applicants respectfully submit that the rejection of Claims 23-25 and 29 as allegedly lacking enablement and written description is based on a misapprehension of the scope of the claims. Claim 23 is directed to "[a] composition, comprising a pharmaceutically acceptable carrier and an amount of a compound effective to inhibit phosphotidylinositol (PI)3-kinase activity," and Claim 29 is directed to "[a] method for inhibiting phosphotidylinositol (PI)3-kinase activity" in a subject. As such, applicants do not need to enable use of a modulator of (PI)3-kinase in any disease or condition, as that is not what is claimed. Rather, Claims 23-25 and 29, describe methods and compositions for PI3-K inhibition comprising administration of an amount of a compound of Formula (1) to a human or animal subject in need thereof. Applicants have shown utility, enablement, and provide adequate written description for administration of the PI3-K inhibitor compounds of Formula (1) (see pages 47-54 of the present application for a lengthy discussion on methods of administration of the claimed compounds). Accordingly withdrawal of the current rejection of Claims 23-25 and 29 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

The Rejection of Claims 35 and 36 Under 35 U.S.C. § 101

Claims 35 and 36 stand rejected under 35 U.S.C. § 101 because the claimed recitation of a use, without setting forth any steps involved in a process, results in an improper definition of a process. Claims 35 and 36 have been canceled. Withdrawal of the rejection is respectfully requested.

The Rejection of Claim 1 Under 35 U.S.C. § 102(b)

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Cabaj et al., *J. Org. Chem. 59*:5090-5092. Withdrawal of the rejection is requested for the following reasons.

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Claim 1 has been amended to exclude "substituted and unsubstituted heterocyclyl" from substituents R_2. With this amendment, the compounds described in the Cabaj reference are excluded from the claimed compounds.

Because the cited reference fails to exactly describe the invention as now claimed, the reference is not anticipatory and withdrawal of the rejection is requested. Furthermore, because the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed, the claimed invention is nonobvious in view of the cited reference.

The Rejection of Claim 1 Under 35 U.S.C. § 102(b)

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Bundy et al., *J. Med. Chem. 38*:4161-4163. Withdrawal of the rejection is requested for the following reasons.

Claim 1 has been amended to exclude "substituted and unsubstituted heterocyclyl" from substituents R_2 and "C_1-C_6 alkyl" from substituents Y. With these amendments, the compounds described in the Bundy reference are excluded from the claimed compounds.

Because the cited reference fails to exactly describe the invention as now claimed, the reference is not anticipatory and withdrawal of the rejection is requested. Furthermore, because the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed, the claimed invention is nonobvious in view of the cited reference.

The Rejection of Claim 1 Under 35 U.S.C. § 102(e)

Claim 1 stands rejected under 35 U.S.C. § 102(e) as being anticipated by Chaudhari et al., WO 02/36586. Withdrawal of the rejection is requested for the following reasons.

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Claim 1 has been amended to exclude "-NH_2" from substituents W. With this amendment, the compounds described in the Chaudhari reference are excluded from the claimed compounds.

Because the cited reference fails to exactly describe the invention as now claimed, the reference is not anticipatory, and withdrawal of the rejection is requested.

The Rejection of Claim 1 Under 35 U.S.C. § 103(a)

Claim 1 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 01/72745 (Fischer et al.). Withdrawal of the rejection is requested for the following reasons.

Claim 1 has been amended to exclude "-NHR" from substituents W. With this amendment, the compounds described in the Fischer reference are excluded from the claimed compounds. The compounds described in the cited reference are N-phenyl-2-pyrimidine compounds that have been surprising found to inhibit cyclin-dependent kinase enzymes (CDKs). See page 1, lines 19-23. Each of the described compounds has an -NH-linked phenyl substituent (-NHPh) at position 2 of the pyrimidine; a dominant structural feature of these compounds. See, for example, Compounds 1-119 in Figure 1 of the reference.

The claimed compounds and those of the cited reference are substituted pyrimidine compounds. However, none of the compounds of the claimed invention include a 2-NHPh substituent, a dominant feature of the compounds described in the cited reference. Although the 2-amino pyrimidine compounds of the cited reference are described only as having a secondary amino link (i.e., -NH- only), the claimed compounds include only a tertiary amino substituent: N-heterocyclyl or -N(R^{1w}, R^{2w}), where R^{1w} and R^{2w} are limited to substituents other than hydrogen (see definition of W in Claim 1).

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The 2-NHPh pyrimidine compounds of the cited reference simply fail to teach, suggest, or provide any motivation to make the tertiary amino substituted compounds of the claimed invention.

Additionally, the compounds of the present invention exhibit potent PI3-K inhibitory activity, whereas those in Fisher et al. are directed to highly selective cyclin0dependent kinase enzyme (CDK) inhibitors (see Table 1, page 57). "Chemical cases should not be decided solely on the basis of homology or analogy in structural formulae. The determination of obviousness is no the mechanistic overlaying of chemical formulae to observe whether a difference greater than a methylene group or a chlorine atom exists. An unobvious property inherent in the claimed compounds is sufficient to overcome a showing of a very close structural obviousness, and there is no basis in law for ignoring any property. Claims to chemical compounds are drawn to more than structural formulae. they define the compounds themselves and compounds possess properties which must be considered along with the formulae." *In re Ruschig*, 52 C.C.P.A. 1238 (C.C.P.A.,1965).

Because the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed, the claimed invention is nonobvious and patentable over the cited reference.

The Rejection of Claim 1 Under 35 U.S.C. § 103(a)

Claim 1 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 02/36586 (Chaudhari et al.) Withdrawal of the rejection is requested for the following reasons.

As noted above, Claim 1 has been amended to exclude "-NH_2" from substituents W. With this amendment, the compounds described in the Chaudhari reference are excluded from the claimed compounds. The compounds described in the cited reference each have an

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amino-linked quinoline (4-aminoquinoline) substituent at position 4 of the pyrimidine; a dominant structural feature of these compounds. See, for example, Examples 1-125 in Table 1 of the reference.

The cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed compounds for at least two reasons: (1) the claimed compounds are structurally dissimilar to those of the cited reference and (2) the claimed compounds and the compounds of the cited reference have diverse uses.

The claimed compounds and those of the cited reference are substituted pyrimidine compounds. However, that is where their structural similarities end. None of the compounds of the claimed invention include a 4-aminoquinoline substituent, a dominant feature of the compounds described in the cited reference. In addition to the 4-aminoquinoline substituent, each and every compound of the cited reference also includes a 2-amino ($-NH_2$) substituent. As noted above, the claimed compounds do not include this structural feature. The 2-amino-4-(4-aminoquinoline)pyrimidine compounds of the cited reference simply fail to teach, suggest, or provide any motivation to make the claimed compounds, which include neither a 2-amino substituent nor a 4-(4-aminoquinoline) substituent.

Furthermore, in addition to their structural dissimilarities, applicants submit that one skilled in the art would not be motivated by the teaching of the cited reference directed to 2-amino-4-(4-aminoquinoline)pyrimidine compounds as N-Type calcium channel antagonists for the treatment of pain to arrive at the claimed compounds useful for inhibiting phosphotidylinositol (PI) 3-kinase activity.

Because the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed, the claimed invention is nonobvious and patentable over the cited reference.

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CONCLUSION

In view of the above amendments and foregoing remarks, applicants believe that Claims 1-34 and 37-43 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

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